

MATTERS ARISING

Diagnosis of genital human papillomavirus lesions in the male

In an excellent study by Hippeläinen *et al*¹ the histopathological criteria for HPV infection were evaluated. As the authors point out HPV DNA may be detected in tissue lacking histopathological HPV associated signs and so can also the opposite situation occur.

Out of the HPV DNA negative biopsies (in situ hybridisation (ISH) technique) 26.7% did show koilocytosis, a sign said to be linked to a replicative HPV infection. The conclusion that koilocytosis is the strongest predictor for HPV positivity in flat genital lesions, giving a risk ratio of 3.7, is worthy of note but it would be interesting to hear the authors further discuss the finding of koilocytosis in the HPV DNA negative patients and the completely normal histology in the adjacent biopsied area. Were no pathological signs found at all? HPV are known to be latent in clinically normal tissue.²

As for the characteristic vacuolisation, also mentioned to be associated to HPV infection, maybe it should be discussed since it could be misinterpreted as koilocytosis by the pathologists not familiar with the signs of HPV infection. In the study referred to vacuolisation was more frequent in HPV negative cases than in HPV positive ones. This inverse correlation is only noticeable in table 4 but is for certain of interest. The authors conclude that HPV typing is essential for diagnosis in doubtful cases (lacking koilocytosis). We want to point out the fact that there is a diagnostic difficulty also in the case where koilocytosis is present and the rather insensitive ISH is negative.

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- 1 Hippeläinen MI, Syrjänen S, Hippeläinen MJ, Saarikoski S, Syrjänen K. Diagnosis of genital human papillomavirus (HPV) lesions in the male: correlation of peniscopy, histology and in situ hybridisation. *Genitourin Med* 1993;69:346-51.
- 2 Ferenczy A, Mitao M, Nagai N, Silverstein SJ, Crum CP. Latent papillomavirus and recurring genital warts. *N Engl J Med* 1985;313:784-8.

Hippeläinen *et al* reply:

While opening the discussion about our recent paper,¹ Drs Strand and Rylander focused on an important issue; the concordance between histology and HPV DNA typing in genital HPV lesions. Indeed, the sometimes low concordance between these two techniques as a source of diagnostic problems has been emphasised in the female genital lesions as well, but according to our experience, such a discordance seems to be an even more severe problem in the diagnosis of genital HPV infections in the males.

In the present series, a type-specific in situ hybridisation (ISH) with seven different

probes (HPV 6,11,16,18,31,33,42) was used as the detection method of HPV DNA.¹ As shown in table 4, the two morphological signs in the biopsies most frequently associated with HPV DNA-positivity were koilocytosis (67.6%) and acanthosis (61.7%). However, these two histological features were detected in HPV DNA-negative biopsies as well, that is, in 26.7% and 40.4% of cases, respectively. As pointed out by Strand and Rylander, koilocytosis is generally accepted as the cytopathic effect of HPV, being the hallmark of a productive HPV infection.

However, in diagnostic studies like this, it is frequently impossible to discover the specific HPV type inducing the koilocytotic change in all tissue biopsies, that is, to achieve a 100% correlation between morphology and presence of HPV DNA. This has multiple reasons. The two most feasible ones to explain the situation in the present series include the following: (1) Of the currently recognised 71 different HPV types, more than 30 are known to infect the genital mucosa. If all these probes are not included in the diagnostic test panel, it is more than probable that a minor or major proportion of the biopsy specimens analysed remain HPV DNA-negative. Our test panel included the seven most frequent HPV types, covering usually some 70% of the HPV-positive samples in most series.² (2) Albeit a highly applicable diagnostic tool, ISH has its limitations, namely, its sensitivity of approximately 20 viral copies/cell. Accordingly, any cell harbouring HPV DNA copies below that limit, most likely remains undetected by ISH. For some unknown reason, the viral load in the male genital HPV lesions seems to be substantially lower than that in the female HPV lesions, which might be one of the reasons why HPV DNA-detection rate by ISH is significantly higher in the latter.

The latter point (2) is also pertinent to the second issue raised by Strand and Rylander; the detection of HPV DNA in histologically normal epithelium. Of the 135 biopsies classified as normal on light microscopy, HPV DNA was found in nine (6.7%) (table 4). This is in agreement with the concept on latent HPV infections, the diagnostic criteria of which were recently outlined in detail.³

The third subject pointed out in their letter is the difficulty in making the distinction between true koilocytes and vacuolised cells. The former are considered as the cytopathic sign of HPV, the latter most probably arise as a result of multiple non-specific stimuli. In fact, such vacuolised cells were rare (6.9%) in HPV DNA-positive lesions, but more frequent (14.7%) in HPV DNA-negative biopsies. We completely agree with Strand and Rylander in their statement that the correct diagnosis of male genital HPV lesions is sometimes difficult both in cases with and without koilocytosis, even if you have ISH in use. It is good to remember, however, that even more difficult problems (albeit of different character) may arise, if more sensitive HPV DNA detection techniques, such as PCR are used.

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- 1 Hippeläinen MI, Syrjänen S, Hippeläinen MJ, Saarikoski S, Syrjänen K. Diagnosis of genital human papillomavirus (HPV) lesions in the male: correlation of peniscopy, histology and in situ hybridization. *Genitourin Med* 1993;69:346-51.
- 2 Kataja V, Syrjänen K, Syrjänen S, *et al*. Prospective follow-up of genital HPV infections: Survival analysis of the HPV typing data. *Eur J Epidemiol* 1990;6:9-14.
- 3 Syrjänen KJ. Genital Human papillomavirus (HPV) infections and their associations with squamous cell cancer: reappraisal of the morphologic, epidemiologic and DNA data. In: Fenoglio-Preiser CM, Wolff M, Rilke F, eds. *Progress in Surgical Pathology*. Field & Wood 1992 Vol XII 217-240.

NOTICES

The UK Family Planning Association

The UK Family Planning Association is beginning a research project to explore the development of recent family planning and reproductive health initiatives within the UK. We particularly wish to gather information from people currently or recently associated with clinical facilities which combine access to family planning information and services with genitourinary medicine and sexual health provision. In the first instance we wish to invite health and social welfare professionals with experience of planning, developing, managing or working in combined clinic services to contact:

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Fifth Congress of the European Academy of Dermatology. 13-17 October 1996. Lisbon, Portugal

Further information may be obtained from: Professor A. Cabral Ascensão, Clínica Universitária de Dermatologia e Venereologia, Hospital Pulido Valente, Alameda das Linhas de Torres, 1700 Lisboa, Portugal.

IUVDT World STD/AIDS Congress 1995. 19-23 March 1995, Singapore

For further information contact: Communication Consultants, 336 Smith Street #06-302, New Bridge Centre, Singapore 0105. Telephone (65) 227 9811. Fax (65) 227 0257.